November 14, 2003

Mr. Mike Leavitt, Administrator
U.S. EPA
P.O. Box 1473
Merrifield, VA 22116

Attn: Chemical Right-to-Know Program

RE: HPV Chemical Challenge Program, AR-201

Dear Mr. Leavitt:

This letter is submitted by Eastman Chemical Company ("Eastman") in response to comments received from the Environmental Protection Agency ("EPA") dated November 12, 2003 following EPA's review of the test plan and robust summaries for Dimethyl 1,4-cyclohexanedicarboxylate (DMCD; CAS No.: 94-60-0). I would like to thank the EPA for its review and welcome the recognition of its completeness and fulfillment of Eastman's obligation to this chemical in the HPV program.

SUMMARY OF EPA COMMENTS

The sponsor, Eastman Chemical Company, submitted a test plan and robust summaries to EPA for dimethyl 1,4-cyclohexanedicarboxylate (DMCD; CAS No. 94-60-0) dated June 17, 2003. EPA posted the submission on the ChemRTK HPV Challenge Web site on July 14, 2003. The submission also includes data for the pure *trans* isomer (CAS No. 3399-22-2) and the structural analog 1,4-cyclohexanedicarboxylic acid (CHDA; CAS No. 1076-97-7).

EPA has reviewed this submission and has reached the following conclusions:

1. Physicochemical Properties. The submitter needs to provide measured vapor pressure and water solubility data following OECD guidelines.

The data submitted by Eastman Chemical Company for these two endpoints was derived by EPIWIN modeling and is believed to fulfill the physicochemical endpoints. This conclusion is based on the statement in the EPA document entitled The Use of Structure-Activity Relationships (SAR) in the high Production Volume Chemicals Challenge Program which reads "In the event that neither measured data nor reference book values are available, estimations using and appropriate model will be accepted for all physicochemical endpoints."

2. Environmental Fate. The submitter needs to add 28-day values to the biodegradation summary.

Data have been added.

3. Health Effects. Adequate data are available for all SIDS-level endpoints for the purposes of the HPV Challenge Program. The submitter needs to address a few deficiencies in the robust summaries.

Various deficiencies have been appropriately addressed.

4. Ecological Effects. The data provided for fish, aquatic invertebrate, and aquatic plants are adequate.

EPA COMMENTS ON THE DIMETHYL 1,4-CYCLOHEXANEDICARBOXYLATE CHALLENGE SUBMISSION

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

The data provided by the submitter for melting point, boiling point, and partition coefficient are adequate for the purposes of the HPV Challenge Program. According to OECD guidelines, if the estimated melting point is under 0 °C, then there is no need to provide measured data for this endpoint.

Vapor pressure. The submitter provided an estimated value of 0.0822 mm Hg (10.96 Pa). Estimated values over 10^{-5} Pa are not adequate for the purposes of the HPV Challenge Program. The submitter needs to provide measured data for this endpoint following OECD guidelines.

See response above.

Water solubility. The submitter provided an estimated value of 688.7 mg/L. An estimated value is not adequate for the purposes of the HPV Challenge Program. The submitter needs to provide measured data for this endpoint following OECD guidelines.

See response above.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

The data provided by the submitter for photodegradation, stability in water and fugacity are adequate for the purposes of the HPV Challenge Program.
Biodegradation. The submitter provided biodegradation data following OECD Guideline 301 B for a 35-day test. As the guideline test duration is 28 days, the submitter needs to include 28-day values in the summary.

A value has been added to the robust summary.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

Adequate data are available for acute, reproductive and developmental toxicities on DMCD and for repeated-dose and genetic toxicities on the structural analog CHDA for the purposes of the HPV Challenge Program. In general, the justification for the use of the acid as an analog for the diester appears to be reasonable. However, the submitter needs to provide reference citations for the various points specified below.

(1) The test plan (p. 4) indicated that, in biological systems, the analog would be expected to be a demethylation product of the sponsored compound, based on similar findings for other short-to-medium length alkyl chain esters located at the one and four positions. The justification included several examples of cleavage of methyl units or ethylhexyl units from 1,4 diesters, but did not include any reference citations for these data.

References have been added to the test plan for these diesters.

(2) The test plan (p. 5) indicated acute oral LD_{50} values for the analog (1,903 mg/kg for males and 2,263 mg/kg for females, respectively), but no robust summary or reference citation was provided.

A reference for these studies was added to the table. The acute study was not summarized as it was not used as a surrogate for that endpoint.

The submitter also needs to address a few deficiencies in the robust summaries.

Ecological Effects (fish, invertebrates, and algae)

The data provided for fish, daphnia, and green algae are adequate. However, the sponsor needs to provide missing water quality parameters.

Information has been added.

Specific Comments on the Robust Summaries

Health Effects

The purity of the test material was missing for acute and genetic toxicity studies.

The robust summaries already state that purity data are not available.

Acute toxicity. A robust summary for an acute oral toxicity study in rats exposed to DMCD was missing the gavage vehicle (if used) and the method for calculating the LD_{50}.

Information has been added to the summary to address these two concerns.

Reproductive and developmental toxicity. A robust summary for a GLP-compliant reproductive/developmental toxicity screening assay in rats exposed to DMCD in feed was missing the parental tissues that were evaluated for histopathology and the magnitudes of the reductions in feed consumption and body weight observed in parental males. The latter information is needed to determine whether the assignment of NOAEL values for parental males was justified.

The organs examined by histology have been noted. The NOAEL listed in the summary was assigned by the study director.

Ecological Effects

Fish. The acute fish toxicity study summary was missing information on water chemistry measurements such as hardness and pH, as well as effects seen and number of fish affected at each concentration. These missing details need to be added to the summary.

The summary has been updated with the requested data.

Invertebrates. The acute invertebrate toxicity study summary was missing information on water chemistry measurements such as hardness and pH; on test group size; and on effects seen and number of daphnids affected at each concentration. These missing details need to be added to the summary.

The summary has been updated with the requested data.

Algae. In the algal toxicity study summary, pH was reportedly measured, but values were not reported in the summary. These pH values should be reported in the summary.

The summary already contains the requested data.

Enclosed with this letter is a computer diskette containing the modified test plan and robust summaries in Adobe Acrobat (.pdf) format. The HPV registration number for Eastman Chemical Company is

Sincerely,

James A. Deyo, D.V.M., Ph.D., D.A.B.T.
Senior Technical Associate

Enclosure